REMARKS

Applicants respectfully request reconsideration of this application, and reconsideration of the Office Action dated August 27, 2003 (Paper No. 22). Upon entry of this Amendment, claims 1-3, 6-9, 11-22, and 24-39 will remain pending in this application with claims 26-30 being withdrawn. Claims 4 and 5 are canceled by this Amendment. The changes to the claims are fully supported by the specification and original claims. No new matter is incorporated by this paper.

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Claims 1-9, 11-22, 24, 25, and 31-39 are rejected under 35 U.S.C. § 112, first paragraph, as purportedly not being fully enabled by the specification. Applicants respectfully traverse.

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? This has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wand*s, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). See M.P.E.P. § 2164.01.

The Office Action asserts that the specification is not enabling for the diagnosis and treatment of all human and animal conditions. However, the claimed invention, currently under consideration, involves a reagent having at least three described functional parts and not a method of diagnosing or treatment. The specification teaches those of ordinary skill in the art how to make and/or use the claimed invention as a reagent. Furthermore, there

are demonstrative examples to guide the skilled practitioner through the production of such reagents.

The Office Action has raised no substantial evidence or analysis to challenge the presumption of enablement. The allegation that the claimed compound can consist of too many different constituent combinations is without support and does not adequately establish undue experimentation. Moreover, " [a]n applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention." *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1344 [60 USPQ2d 1851] (Fed. Cir. 2001). To maintain this rejection the Office Action must disclose persuasive evidence, with a detailed analysis, to demonstrate the reasoning as to why the specification would not enable one of ordinary skill in the art to practice the claimed invention without undue experimentation.

There is clearly sufficient disclosure in the specification as to how the invention may be practiced. It is reasonable to conclude that the specification does teach how to practice the invention according to the full extent claimed. The Office Action has not set forth evidence or scientific reasoning as to why the rejected claims are not enabled by the specification, and accordingly, Applicant respectfully traverses the rejection and requests that it be withdrawn

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Claims 1-9, 11-22, 24, 25, and 31-39 are rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite.

The Office Action asserts the terminology "capable of" in claims 1 and 11 is indefinite. In response, the claim 1 has been amended to recite "said affinity ligand binds" and "forming a covalent bond." In addition, claim 11 has been amended to recite "enzymes that convert."

The Office Action also asserts that term derivative is indefinite. Applicants again respectfully submit that claims 1 and 30 define the term derivative as "a derivative of avidin or streptavidin having essentially the same binding function to the affinity ligand." Hence, the term "derivative" does not encompass an innumerable number of chemicals, but encompasses derivatives of avidin or streptavidin (which derivatives are known to those of ordinary skill) that have essentially the same binding function to the affinity ligand (e.g. biotin) as do avidin or streptavidin. Accordingly, those of ordinary skill in the art would fully understand the metes and bounds of the term derivative as defined in the claims

The Office Action further asserts that claims 33 is indefinite in the recitation of "cyclohexy;-DTPA." In response, claim 33 has been corrected to recite "cyclohexyl-DTPA."

In view of the above remarks, Applicants submit that this rejection is overcome. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

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Claims 1-5, 8, 9, 11-15, 17-19, 21, 22, 24, 31, 35, 36, 38, and 39 are rejected under 35 U.S.C. § 102(a) as anticipated by Wilbur et al. (WO 97/29114). The Office Action asserts that Wilbur describes every feature of the claimed invention. Applicants respectfully traverse.

The Office Action asserts that compound No. 56 on page 39 in Wilbur includes all of the features in the claims. The Office Action states that alphacarboxylate is provided in linker 1. However, this is not correct for compound 56. The carboxyl group in compound 56 is an intrinsic part of the biotin residue and does not belong to linker 1. According to the present invention, the alpha carboxylate is within (part of) linker 1 and is specifically positioned alpha to the biotinamide bond (i.e. alpha-carboxylate) that connects linker 1 with the affinity ligand, i.e. biotin. Thus, according to the present invention, there is a minimum of one carboxyl group present in the linker 1, and that carboxyl group is located

in a specific position. Other carboxyl groups may be present within linker 1 to aid in solubility, or may be at the terminus of linker 1 to form covalent bonds between the linker and the affinity ligand and/or the trifunctional cross-linking reagent. Additionally, compound 56 in the Wilbur patent does not provide any stability towards cleavage by the enzyme biotinidase. Thus, for at least this reason, Wilbur fails to describe each and every feature of independent claim 1 (from which the other claims depend).

Furthermore, claim 1 has been amended to replace the terminology "an amide bond" with a "a biotinamide bond". Moreover, the content of previous claim 5 now has been introduced into claim 1. In other words, claim 1 recites that the affinity ligand is biotin or a biotin derivative. Claim 1 also recites that the biotin derivative refers to those biotin derivatives that retain the ability to bind with avidin and/or streptavidin. Claim 1has also been amended by introduction of the term "covalent." This feature is supported on page 14, upper half, of the specification. These additional features of claim 1 further distinguish the claim from Wilbur.

Wilbur primarily discloses difunctional reagents adapted for non-covalent affinity based linkage to biomolecules, e.g. via biotin-avidin binding. These reagents are intended to be water-soluble and are used for certain applications in cancer therapy but through completely different modalities. In contrast, the present invention refers to trifunctional reagents, which bind covalently to a biomolecule. Compound 56 in the Wilbur reference is only mentioned as a possible reagent and is the only compound of that type presented in the entire document. However, it differs from the trifunctional reagents described in the present invention insofar that it is not stabilized against biotinidase and would hence not be suitable *in vivo*. Stabilization against biotinidase is only disclosed in connection with a difunctional reagent in the Wilbur reference. Moreover, introducing a functional reagent does not necessarily mean that the functionality may be introduced in a trifunctional reagent without affecting the affinity due to steric or other structural features.

In view of the above remarks, Applicants submit that this rejection is overcome. Hence, reconsideration and withdrawal of the rejection are respectfully requested.

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Claims 6, 7, 16, 20, 32, 34, and 37 are rejected under 35 U.S.C. § 103(a) as obvious based on Wilbur et al. Applicants also respectfully traverse this rejection.

The deficiencies of Wilbur are detailed above. Moreover, Applicants provide the following additional remarks. A person skilled in the art would not be guided to the present invention from the teachings of Wilbur. This is because firstly, Wilbur's application is not focused on the type of reagents disclosed in the present application, and secondly, the treatment modalities in which difunctional reagents are used are completely different. Page 17 of Wilbur states that a steric group alpha to the amine provides resistance to cleavage by biotinidase and that such a group may include carboxylate, etc. However, on page 18, Wilbur states that "depending upon the steric bulk of the branching group alpha to the amine (or other) functionality attached to the carboxylate", some reduction in binding affinity for biotin binding proteins may result.

In contrast, the present inventors have surprisingly found that an alpha carboxylation of linker 1 retains the binding affinity in an unforeseeable way. Thus, the above-mentioned statement in the Wilbur document teaches away for a person skilled in the art to try introduction of improved alpha carboxylate in the linker 1 molecule. Applicants enclose herewith a journal article which shows that compounds containing such modifications have been extensively tested. See Wilbur et al. Bioconjugate Chem. 2001, 12, 616-623.

Applicants submit that in view of the above remarks, the rejection is overcome and its withdrawal is respectfully requested.

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Claim 33 is rejected under 35 U.S.C. § 103(a) as obvious based on Wilbur et al. in view of Gansoh et al. (U.S. Pat. No. 5,286,850). Applicants also respectfully traverse this rejection.

The deficiencies of Wilbur are detailed above. In addition, in Wilbur no trifunctional reagent incorporating metal chelates were disclosed. Gansoh fails to remedy the deficiencies. The subject matter of Gansoh relates to difunctional cyclohexyl-DTPA ligands and methods for utilizing such compounds. Gansoh describes various means of directly linking such structures to antibodies, which could be used for therapeutic and diagnostic applications.

Gansoh discusses the importance of using very strong metal chelates to firmly link radiometals to monoclonal antibodies. Gansoh does not disclose any trifunctional regents or any other multifunctional agents. Neither does Gansoh discuss or even mention the issue of blood clearance to improve the therapeutic or diagnostic outcome. Hence, Gansoh does not teach any subject matter related to the present invention apart from presenting one of many types of "effector residues" which could be incorporated in the "Reagent" of the present invention. Furthermore, the direct linkage of the chelate to a "biomolecule" does not guide "anyone skilled in the art" to the present invention.

Applicants submit that in view of the above remarks, the rejection is overcome and its withdrawal is respectfully requested.

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Applicants respectfully submit that this Amendment and the above remarks obviate the outstanding rejections in this case, thereby placing the application in condition for immediate allowance. Allowance of this application is earnestly solicited.

If any fees under 37 C.F.R. §§ 1.16 or 1.17 are due in connection with this filing, please charge the fees to Deposit Account No. 02-4300; Order No. 033700.003.

If an extension of time under 37 C.F.R. § 1.136 is necessary that is not accounted for in the papers filed herewith, such an extension is requested. The extension fee should be charged to Deposit Account No. 02-4300; Order No. 033700.003.

Respectfully submitted,

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